K 09/936024 Copy for the Elected Office (EO/US) PCT/US00/06417

# PATENT COOPERATION TREATY

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From the INTERNATIONAL BUREAU

## PCT

**NOTIFICATION OF THE RECORDING OF A CHANGE**

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

WEBSTER, Thomas, D.
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285
ETATS-UNIS D'AMERIQUE

| | |
|---|---|
| **Date of mailing** (day/month/year)<br>19 September 2001 (19.09.01) | |
| **Applicant's or agent's file reference**<br>X-12799 | **IMPORTANT NOTIFICATION** |
| **International application No.**<br>PCT/US00/06417 | **International filing date** (day/month/year)<br>20 March 2000 (20.03.00) |

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

| Name and Address | State of Nationality | State of Residence |
|---|---|---|
| TSCHANG, Sheng-Hung, Rainbow<br>7381 Freeport Lane, Apartment C<br>Indianapolis, IN 46214<br>United States of America | US | US |
| | Telephone No. | |
| | Facsimile No. | |
| | Teleprinter No. | |

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

| Name and Address | State of Nationality | State of Residence |
|---|---|---|
| TSCHANG, Sheng-Hung, Rainbow<br>4963 Riley Mews<br>Carmel, IN 46033<br>United States of America | US | US |
| | Telephone No. | |
| | Facsimile No. | |
| | Teleprinter No. | |

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

| | |
|---|---|
| **The International Bureau of WIPO**<br>**34, chemin des Colombettes**<br>**1211 Geneva 20, Switzerland** | Authorized officer<br>Catherine MASSETTI |
| Facsimile No.: (41-22) 740.14.35 | Telephone No.: (41-22) 338.83.38 |

PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| Applicant's or agent's file reference | **FOR FURTHER ACTION** | see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. |
|---|---|---|
| X-12799 | | |
| International application No. | International filing date *(day/month/year)* | (Earliest) Priority Date *(day/month/year)* |
| PCT/US 00/ 06417 | 20/03/2000 | 30/03/1999 |

Applicant

ELI LILLY AND COMPANY et al.

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [X] contained in the international application in written form.

   [X] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

   [X] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

# INTERNATIONAL SEARCH REPORT

International Application No
[redacted]/US 00/06417

**A. CLASSIFICATION OF SUBJECT MATTER**
IPC 7 C12N15/12 C12N15/62 C07K14/705 C12P21/02 A61K38/17
A61P11/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K C12P A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
STRAND, EMBL, EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, EMBASE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | √ WO 98 30694 A (HUMAN GENOME SCIENCES INC ;FENG PING (US); NI JIAN (US); EBNER REI) 16 July 1998 (1998-07-16)<br><br>page 4, line 8-27<br>page 9, line 3-11<br>page 22, line 26 -page 33, line 17<br>example 1<br>figures 3-5<br>---<br>-/-- | 1,3-5,8, 9,17,19, 21, 25-27, 29,31, 33,35, 37, 39-44, 47-50 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 19 September 2000 | 29/09/2000 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | van de Kamp, M |

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 99 14330 A (GENENTECH INC)<br>25 March 1999 (1999-03-25)<br><br>page 8, line 31-42<br>page 12, line 23 -page 14, line 13<br>page 15, line 43 -page 16, line 36<br>figure 4; example 1<br>examples 7,9 | 2,4,6,8,<br>9,17,19,<br>21,<br>25-27,<br>29,31,<br>33,35,<br>38,40,<br>42-44,<br>47-50 |
| X | WO 99 04001 A (ZYMOGENETICS INC)<br>28 January 1999 (1999-01-28)<br><br>page 31, line 24 -page 33, line 2<br>page 43, line 8 -page 44, line 2<br>page 44, line 32 -page 45, line 4<br>examples 3-5<br>claims 1,2,5,6 | 8,9,26,<br>43,44,<br>47-50 |
| A | PITTI ET AL: "Genomic amplification of a decoy receptor for FAS ligand in lung and colon cancer"<br>NATURE,<br>vol. 396, 17 December 1998 (1998-12-17),<br>pages 699-703, XP002139977<br>abstract | |
| E | WO 00 34782 A (SONG HO YEONG ;SU ERIC WEN (US); LILLY CO ELI (US); ROSTECK PAUL R)<br>15 June 2000 (2000-06-15)<br><br>page 3, line 13 -page 9, line 17<br>example 9<br>claims 3,19 | 1,4,5,<br>25,29,<br>33,37,<br>40-44,<br>47-50 |
| T | SHEIKH M S ET AL.: "Death and decoy receptors and p53-mediated apoptosis"<br>LEUKEMIA,<br>vol. 14, no. 8, August 2000 (2000-08),<br>pages 1509-1513, XP000946082<br>abstract | |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
US 00/06417

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 9830694 A | 16-07-1998 | AU 5815798 A | 03-08-1998 |
| | | AU 6238698 A | 03-08-1998 |
| | | BR 9806954 A | 21-03-2000 |
| | | CN 1247567 T | 15-03-2000 |
| | | EP 1007659 A | 14-06-2000 |
| | | EP 0990031 A | 05-04-2000 |
| | | WO 9830693 A | 16-07-1998 |
| WO 9914330 A | 25-03-1999 | AU 9497098 A | 05-04-1999 |
| | | EP 1015587 A | 05-07-2000 |
| WO 9904001 A | 28-01-1999 | AU 9013998 A | 10-02-1999 |
| WO 0034782 A | 15-06-2000 | AU 2164400 A | 26-06-2000 |
| | | EP 1020521 A | 19-07-2000 |

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organizati n
International Bureau

(43) International Publication Date
5 October 2000 (05.10.2000)

PCT

(10) International Publication Number
WO 00/58465 A3

(51) International Patent Classification[7]: C12N 15/12, 15/62, C07K 14/705, C12P 21/02, A61K 38/17, A61P 11/00

(21) International Application Number: PCT/US00/06417

(22) International Filing Date: 20 March 2000 (20.03.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

| | | |
|---|---|---|
| 60/126,839 | 30 March 1999 (30.03.1999) | US |
| 60/140,077 | 21 June 1999 (21.06.1999) | US |
| 60/140,156 | 21 June 1999 (21.06.1999) | US |
| 60/160,566 | 20 October 1999 (20.10.1999) | US |
| 60/183,398 | 18 February 2000 (18.02.2000) | US |

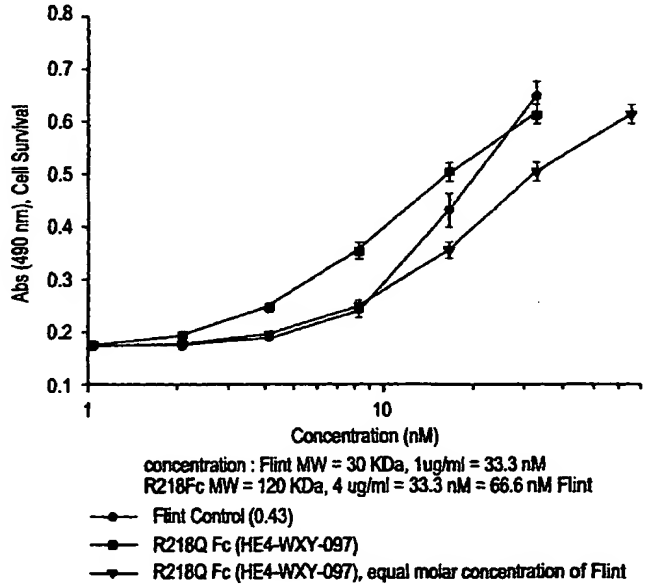
(71) Applicant *(for all designated States except US)*: **ELI LILLY AND COMPANY** [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BECKER, Gerald, Wayne** [US/US]; 10815 East 121st Street, Fishers, IN 46038 (US). **COHEN, Fredric, Jay** [US/US]; 15 Autumn Drive, Newtown, PA 18940 (US). **GONZALEZ-DEWHITT, Patricia, Ann** [US/US]; 12121 East 191st Street, Noblesville, IN 46060 (US). **HALE, John, Edward** [US/US]; 7644 Forest Drive, Fishers, IN 46038 (US). **MICANOVIC, Radmila** [US/US]; 7126 White Oak Trail, Indianapolis, IN 46236 (US). **NEWTON, Christy, Michelle** [US/US]; 7908 Meadow Bend Circle, Indianapolis, IN 46259 (US). **NOBLITT, Timothy, Wayne** [US/US]; 2650 Manker, Indianapolis, IN 46203 (US). **RATHMACHALAM, Radhakrishnan** [IN/US]; 3793 Lattice Court, Carmel, IN 46032 (US). **TSCHANG, Sheng-Hung, Rainbow** [US/US]; 7381 Freeport Lane, Apartment C, Indianapolis, IN 46214 (US). **WITCHER, Derrick, Ryan** [US/US]; 10898 Parrot Court, Fishers, IN 46038 (US). **WROBLEWSKI, Victor, John** [US/US]; 1466 Woodpond South Roundabout, Carmel, IN 46033 (US).

*[Continued on next page]*

(54) Title: FLINT POLYPEPTIDE ANALOGS




(57) Abstract: Disclosed are polypeptide analogs of FLINT, polydeoxynucleotides encoding FLINT analogs, and methods of using FLINT analogs and polydeoxynucleotides. The FLINT analogs of the invention include polypeptides having the amino acid sequence of FLINT, modified at one or more positions with amino acid substitutions, and include fragments thereof, as well as Fc fusions comprising FLINT and FLINT analogs.

WO 00/58465 A3

(74) **Agents: WEBSTER, Thomas, D.** et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).

(81) **Designated States** *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) **Designated States** *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published:**
— *With international search report.*

**(88) Date of publication of the international search report:**
25 January 2001

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/06417

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/12 C12N15/62 C07K14/705 C12P21/02 A61K38/17
A61P11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K C12P A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
STRAND, EMBL, EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 98 30694 A (HUMAN GENOME SCIENCES INC ;FENG PING (US); NI JIAN (US); EBNER REI) 16 July 1998 (1998-07-16)<br><br>page 4, line 8-27<br>page 9, line 3-11<br>page 22, line 26 -page 33, line 17<br>example 1<br>figures 3-5<br><br>-/-- | 1,3-5,8, 9,17,19, 21, 25-27, 29,31, 33,35, 37, 39-44, 47-50 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 19 September 2000 | 29/09/2000 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | van de Kamp, M |

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 99 14330 A (GENENTECH INC)<br>25 March 1999 (1999-03-25)<br><br>page 8, line 31-42<br>page 12, line 23 -page 14, line 13<br>page 15, line 43 -page 16, line 36<br>figure 4; example 1<br>examples 7,9 | 2,4,6,8,<br>9,17,19,<br>21,<br>25-27,<br>29,31,<br>33,35,<br>38,40,<br>42-44,<br>47-50 |
| X | WO 99 04001 A (ZYMOGENETICS INC)<br>28 January 1999 (1999-01-28)<br><br>page 31, line 24 -page 33, line 2<br>page 43, line 8 -page 44, line 2<br>page 44, line 32 -page 45, line 4<br>examples 3-5<br>claims 1,2,5,6 | 8,9,26,<br>43,44,<br>47-50 |
| A | PITTI ET AL: "Genomic amplification of a decoy receptor for FAS ligand in lung and colon cancer"<br>NATURE,<br>vol. 396, 17 December 1998 (1998-12-17),<br>pages 699-703, XP002139977<br>abstract | |
| E | WO 00 34782 A (SONG HO YEONG ;SU ERIC WEN (US); LILLY CO ELI (US); ROSTECK PAUL R)<br>15 June 2000 (2000-06-15)<br><br>page 3, line 13 -page 9, line 17<br>example 9<br>claims 3,19 | 1,4,5,<br>25,29,<br>33,37,<br>40-44,<br>47-50 |
| T | SHEIKH M S ET AL.: "Death and decoy receptors and p53-mediated apoptosis"<br>LEUKEMIA,<br>vol. 14, no. 8, August 2000 (2000-08),<br>pages 1509-1513, XP000946082<br>abstract | |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int[illegible]l Application No
PCT/US 00/06417

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 9830694 A | 16-07-1998 | AU 5815798 A | 03-08-1998 |
| | | AU 6238698 A | 03-08-1998 |
| | | BR 9806954 A | 21-03-2000 |
| | | CN 1247567 T | 15-03-2000 |
| | | EP 1007659 A | 14-06-2000 |
| | | EP 0990031 A | 05-04-2000 |
| | | WO 9830693 A | 16-07-1998 |
| WO 9914330 A | 25-03-1999 | AU 9497098 A | 05-04-1999 |
| | | EP 1015587 A | 05-07-2000 |
| WO 9904001 A | 28-01-1999 | AU 9013998 A | 10-02-1999 |
| WO 0034782 A | 15-06-2000 | AU 2164400 A | 26-06-2000 |
| | | EP 1020521 A | 19-07-2000 |

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
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| **CG** | Congo | **KE** | Kenya | **NL** | Netherlands | **YU** | Yugoslavia |
| **CH** | Switzerland | **KG** | Kyrgyzstan | **NO** | Norway | **ZW** | Zimbabwe |
| **CI** | Côte d'Ivoire | **KP** | Democratic People's Republic of Korea | **NZ** | New Zealand | | |
| **CM** | Cameroon | | | **PL** | Poland | | |
| **CN** | China | **KR** | Republic of Korea | **PT** | Portugal | | |
| **CU** | Cuba | **KZ** | Kazakstan | **RO** | Romania | | |
| **CZ** | Czech Republic | **LC** | Saint Lucia | **RU** | Russian Federation | | |
| **DE** | Germany | **LI** | Liechtenstein | **SD** | Sudan | | |
| **DK** | Denmark | **LK** | Sri Lanka | **SE** | Sweden | | |
| **EE** | Estonia | **LR** | Liberia | **SG** | Singapore | | |

09/936021

Translation

3

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| | | |
|---|---|---|
| Applicant's or agent's file reference<br>340643/17676 | **FOR FURTHER ACTION** | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
| International application No.<br>PCT/FR00/00558 | International filing date (*day/month/year*)<br>07 March 2000 (07.03.00) | Priority date (*day/month/year*)<br>08 March 1999 (08.03.99) |
| International Patent Classification (IPC) or national classification and IPC<br>H01S 5/026 | | |
| Applicant<br>FRANCE TELECOM | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| | |
|---|---|
| Date of submission of the demand<br>02 October 2000 (02.10.00) | Date of completion of this report<br>28 June 2001 (28.06.2001) |
| Name and mailing address of the IPEA/EP<br><br>Facsimile No. | Authorized officer<br><br>Telephone No. |

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FR00/00558

## I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:

pages 1-3, 5-10, as originally filed
pages _____, filed with the demand
pages 4, 4a, filed with the letter of 04 April 2001 (04.04.2001)

☒ the claims:

pages 2-19, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages 1, filed with the letter of 04 April 2001 (04.04.2001)

☒ the drawings:

pages 1/3-3/3, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 1-19 | YES |
| | Claims | | NO |
| Inventive step (IS) | Claims | 1-19 | YES |
| | Claims | | NO |
| Industrial applicability (IA) | Claims | 1-19 | YES |
| | Claims | | NO |

2. Citations and explanations

1. Reference is made to the following documents:

D1: US-A-4 054 363 (SUEMATSU YASUHARU) 18 October 1977 (1977-10-18)

D2: CHUANG Z M ET AL: 'PHOTONIC INTEGRATED TUNABLE RECEIVERS WITH OPTICAL PREAMPLIFIERS FOR DIRECT DETECTION' APPLIED PHYSICS LETTERS, US, AMERICAN INSTITUTE OF PHYSICS. NEW YORK, vol. 63, no. 7, pages 880-882.

2. Document D1 describes an optoelectronic system (Figure 16, Column 4, lines 54-56) which includes at least three sections 10, 20 and 50 corresponding to specific respective functions (namely, a laser 10, a waveguide 20 and a modulator 50). D1 also describes a method for producing such a system. The forbidden band energy of sections 10 and 50 differs from that of section 20 (Figure 5, Column 3, lines 3-17). The sections consist of a plurality of layers placed one on top of the other using epitaxy (Column 1, lines 58-59). The upper layer is etched to define sections 10 and 50 (Column 4, lines 2-4). Sections 10 and 50 are limited within the upper layer and section 20 is defined in the lower layer. The structure

enables evanescent coupling between sections 10 and 50 and section 20.

The subject matter of Claims 1 and 15 differs from the known system and method in that the intermediate section includes a grating and the coupling coefficient K of the grating is such that the product KL (L represents the length of the intermediate section) is around 1.

It is well known in this field to use a grating to improve evanescent coupling (for example, D2, page 881, left-hand column, line 17, Figure 2). However, none of the documents cited in the preliminary search report gives an indication of selecting the coupling coefficient of the grating in the intermediate section so that KL is around 1. Therefore, the solution according to Claims 1 and 15 is not obvious.

Claims 2-14 and 16-19 describe advantageous embodiments of the subject matter of Claims 1 and 15, respectively. Therefore, the subject matter of said claims is novel and involves an inventive step.

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:

1. Claim 1 has been drafted in the two-part form. However, some features should not appear in the characterising part since they are disclosed in document D1 in combination with the features set forth in the preamble (PCT Rule 6.3(b)).

# PATENT COOPERATION TREATY



From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

WEBSTER, Thomas D. et al
ELI LILLY AND COMPANY
Lilly Corporate Center
Indianapolis Indiana 46285
ETATS-UNIS D'AMERIQUE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 13.06.2001 |
| Applicant's or agent's file reference<br>X-12799 | **IMPORTANT NOTIFICATION** |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US00/06417 | 20/03/2000 | 30/03/1999 |

Applicant
ELI LILLY AND COMPANY et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

| Name and mailing address of the IPEA/ | Authorized officer |
|---|---|
| European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Zoglauer, H<br><br>Tel.+49 89 2399-8051 |

Form PCT/IPEA/416 (July 1992)

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| X-12799 | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/US00/06417 | 20/03/2000 | 30/03/1999 |
| International Patent Classification (IPC) or national classification and IPC<br>C12N15/12 | | |
| Applicant<br>ELI LILLY AND COMPANY et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1-7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 02/10/2000 | 13.06.2001 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized officer<br>Paresce, D<br>Telephone No. +49 89 2399 8995 |

Form PCT/IPEA/409 (cover sheet) (January 1994)

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/06417

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
**Description, pages:**

1-90 as originally filed

**Claims, No.:**

1-20 with telefax of 26/04/2001

**Drawings, sheets:**

1/2,2/2 as originally filed

**Sequence listing part of the description, pages:**

1-3, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   *(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-20 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | 1-20 |
| | No: | Claims | |
| Industrial applicability (IA) | Yes: | Claims | 1-20 |
| | No: | Claims | |

2. Citations and explanations
   **see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
**see separate sheet**

**Re Item I**

**Basis of the report**

This International Preliminary Examination Report is based on amended claims 1-20 submitted by a telefax, received on 26.04.01. The amended set of claims is supported by the original disclosure and therefore complies with the requirements of Article 34(2)(b) PCT.

**Re Item V**

**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1) The documents mentioned in this communication are numbered as in the search report, i.e. D1 corresponds to the first document of the search report.

2) **Novelty: Article 33(2) PCT**

D1 describes the human Tumor Necrosis Factor Receptor (TNFR)-6α and 6β proteins. TNFR-6α is identical to FLINT of the present application (see figure 1 of D1). D1 discloses TNFR-6α proteins, nucleic acid molecules encoding human TNFR-6α, vectors, host cells, recombinant methods of producing TNFR-6α, and diagnostic and therapeutic methods involving the use of TNFR-6α proteins (see abstract). D1 also describes variant and mutant TNFR-6α polypeptides. Recombinant DNA techniques to create mutant proteins including single or multiple amino acid substitutions, deletions, additions or fusion proteins are described. For example, N-terminal and C-terminal deletion mutants are described (see p. 24), as well as various mutant TNFR-6α proteins with amino acid substitutions (see p. 25-32). D1 describes the use of amino acid substitutions to produce proteins with desirable improved characteristics such as improved solubility or altered ligand selectivity. Furthermore, D1 discloses fusion proteins formed by combining the TNFR-6α polypeptides and an IgG Fc fusion region peptide to increase the half-life of the polypeptide (see p. 26, 33). Example 3a of D1 describes the cloning and expression of a TNFR-6α-HA fusion protein (see p. 57).

D2 discloses a TNFR homolog called DcR3. DcR3 is identical to FLINT of the present application. D2 discloses nucleic acid molecules encoding DcR3, chimeric molecules and antibodies to DcR3 (see abstract). D2 describes covalent modifications of the DcR3 including adding glycosylation sites to the protein and fusing the DcR3 protein with a tag polypeptide or an immunoglobulin or to the Fc region of an IgG molecule (see p.12-14). D2 also describes methods for introducing nucleotide changes in the DcR3 DNA or amino acid sequence (see p. 15-16). Example 1 of D2 discloses various EST sequences for DcR3 (see p. 36-37) and examples 7-9 disclose a DcR3 polypeptide fused to an epitope tag such as poly-his tags and immunoglobulin tags (Fc regions of IgG).

D3 discloses a TNFR called ZTNFR-5. ZTNFR-5 is also identical to FLINT of the present application. D3 discloses ZTNFR-5 proteins, nucleic acid molecules encoding human ZTNFR-5, vectors, host cells, recombinant methods of producing ZTNFR-5, and diagnostic and therapeutic methods involving the use of ZTNFR-5 proteins (see p. 1-11). D3 also describes methods of making multiple amino acid substitutions in the ZTNFR-5 amino acid sequence (see p. 25-33). D3 discloses soluble ZTNFR-5 receptors used to form fusion proteins with human Ig, or to form His-tagged proteins (see p. 43, example 3).

The subject-matter of claims 1-20 has not been made available to the public by any of the available prior art documents and can therefore be regarded as novel.

2) **Inventive Step: Article 33(3) PCT**

D1, D2 or D3 are regarded as being the closest prior art to the subject-matter of these claims.

The subject-matter of claims 1-20 consists in the provision of polypeptide analogs of FLINT, polynucleotide molecules encoding the FLINT analogs and uses thereof. The FLINT analogs of the present application include polypeptides having the amino acid sequence of FLINT (disclosed in D1, D2 or D3) modified at one or more positions with amino acid substitutions, deletions or additions, and fragments thereof. It is stated on p. 2-3 of the present application that the claimed FLINT analogs are believed to have improved properties compared with FLINT

such as greater potency, longer *in vivo* half lives, decreased aggregation and increased solubility. The present application also claims Fc-FLINT fusion proteins. It is disclosed in the present application that FLINT undergoes proteolysis *in vivo* to produce two peptide fragments. Protease resistant FLINT analogs can be produced that are more resistant to proteolysis between residues 218 and 219 of SEQ ID NO: 1 by one or more amino acid substitutions, deletions or additions of the FLINT full-length sequence (see p. 16-19). It is stated that preferably these changes occur in the region from about position 214 through position 222 of SEQ ID NO:1 (p. 17). The prior art does not disclose the proteolytic processing of FLINT at residue 218 nor that protease resistant FLINT analogs can be produced by mutations of the FLINT amino acid sequence in the region around residue 218.

At the priority date of the present application, FLINT analogs and methods of making mutant FLINT polypeptides had already been disclosed in the prior art. D1, for example, describes several variant and mutant TNFR-6α polypeptides. N-terminal and C-terminal deletion mutants are described (see p. 24), as well as various mutant TNFR-6α proteins with amino acid substitutions (see p. 25-32). D1 describes the use of amino acid substitutions to produce proteins with desirable improved characteristics such as improved solubility or altered ligand selectivity. Furthermore, D1 discloses fusion proteins formed by combining the TNFR-6α polypeptides and an IgG Fc fusion region peptide to increase the half-life of the polypeptide (see p. 26, 33). Example 3a of D1 describes the cloning and expression of a TNFR-6α-HA fusion protein (see p. 57).

The prior art, however, does not disclose the specific analogs of the present application and the IPEA is of the opinion that the subject-matter of claims 1-20 cannot be derived from the available prior art in an obvious manner and therefore complies with the requirements of Article 33(3) PCT.

**Re Item VI**

**Certain documents cited**

Certain published documents (Rule 70.10)

| Application No Patent No | Publication date *(day/month/year)* | Filing date *(day/month/year)* | Priority date *(valid claim)* *(day/month/year)* |
|---|---|---|---|
| WO 00/34782 | 15.06.00 | 07.12.99 | 09.12.98 |

## VIII. Certain observations on the international application

### 1) Clarity: Article 6 PCT

Article 6 PCT requires amongst other things that the claims, which define the matter for which protection is sought (i.e. the object of invention) be clear. This has to be interpreted as meaning not only that a claim from a technical point of view must be comprehensible, but also that it must define clearly the object of the invention, that is to say, it must indicate all the essential features thereof. The essential features are regarded as all features which are necessary to obtain the desired effect, or differently expressed, those features which are necessary to solve the technical problem with which the application is concerned. In other words, all technical features which enable the skilled person to put the claimed matter into practice without undue burden i.e. without experimentation or without application of inventive skill.

In the present case, the subject-matter of claims 11, 13-14 is not disclosed in a manner sufficiently clear and complete for a person skilled in the art to put the claimed matter into practice. Claims 11, 13-14 refer to a "protease-resistant FLINT analog". The use of an internal arbitrary designation of a protein is meaningless to the person skilled in the art and does not constitute a definition through technical means as required by Article 6 PCT. The IPEA considers TNFR-6α, DcR3, ZTNFR-5 to be "FLINT analogs". Furthermore, the term, "protease-resistant" is vague and merely paraphrases the technical problem with which the application is concerned. The claims attempt to define the subject-matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result should be added. The claimed protein must be clearly and unambiguously characterized e.g. by reference to technical features, (sequence information) in order to satisfy the requirements of Article 6 PCT.

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We Claim:

1. A FLINT analog comprising a polypeptide having FLINT biological activity, said polypeptide having the amino acid sequence of SEQ ID NO:1 modified by:
   a) replacing tryptophan at position 53 with aspartic acid;
   b) replacing threonine at position 88 with proline;
   c) replacing alanine at position 107 with serine, aspartic acid, glutamic acid or threonine;
   d) replacing isoleucine at position 110 with threonine or glutamic acid; or
   e) replacing proline at position 104 with serine,
   and physiologically acceptable salts of said polypeptide and said fragment.

2. A FLINT analog comprising a polypeptide having FLINT biological activity, said polypeptide having the amino acid sequence of SEQ ID NO:1 modified by:
   a) replacing alanine at position 2 or position 12 with asparagine;
   b) replacing proline at position 25, position 38, position 126 or position 171 with asparagine;
   c) replacing arginine at position 35 with asparagine;
   d) replacing serine at position 37 with asparagine and proline at position 38 with any other naturally occurring amino acid;
   e) replacing serine at position 166 with asparagine;
   f) replacing leucine at position 172 with asparagine;
   g) replacing aspartic acid at position 194 with asparagine; or
   h) replacing threonine at position 114 with asparagine and proline at position 115 with any naturally occurring amino acid;

and physiologically acceptable salts of said polypeptide and said fragment.

3. A FLINT analog comprising a polypeptide having FLINT biological activity, said polypeptide having the amino acid sequence of SEQ ID NO:1 modified by:

a) replacing asparagine at position 63 with tryptophan;

b) replacing glycine at position 67 with aspartic acid and alanine at position 94 or glycine at position 95 with tyrosine;

c) replacing arginine at position 69 with glutamic acid;

d) replacing arginine at position 82 with glutamic acid or threonine;

e) replacing alanine at position 94 with tryosine and glycine at position 95 with aspartic acid;

f) replacing phenylalanine at position 96 with glutamine;

g) replacing alanine at position 101 with threonine; or

h) replacing glycine at position 95 with aspartic acid;

and physiologically acceptable salts of said polypeptide and said fragment.

4. A FLINT analog comprising a polypeptide having FLINT biological activity, said polypeptide having the amino acid sequence of SEQ ID NO:1 modified by:

a) replacing arginine at position 10 with glutamine, asparagine, serine or threonine, provided that when the replacing amino acid is asparagine, then alanine at position 12 is optionally replaced with serine or threonine;

b) replacing glutamic acid at position 13 with glutamine, asparagine, serine or threonine, provided that when the replacing amino acid is asparagine, then glycine at position 15 is optionally replaced with s rine or thre nine;

c) replacing glutamic acid at position 16 with glutamine, asparagine, serine or threonine, provided that when the replacing amino acid is asparagine, then leucine at position 18 is optionally replaced with serine or threonine;

d) replacing arginine at position 17 with glutamine, asparagine, serine or threonine, provided that when the replacing amino acid is asparagine, then valine at position 19 is optionally replaced with serine or threonine;

e) replacing arginine at position 31 with glutamine, asparagine, serine or threonine, provided that when the replacing amino acid is asparagine, then cysteine at position 33 is optionally replaced with serine or threonine;

f) replacing arginine at position 34 with glutamine, asparagine, serine or threonine, provided that when the replacing amino acid is asparagine, then aspartic acid at position 36 is optionally replaced with serine or threonine;

g) replacing arginine at position 35 with glutamine, asparagine, serine or threonine;

h) replacing aspartic acid at position 36 with glutamine, asparagine, serine or threonine, provided that when the replacing amino acid is asparagine, then proline at position 38 is optionally replaced with serine or threonine;

i) replacing arginine at position 143 with glutamine, asparagine, serine or threonine, provided that when the replacing amino acid is asparagine, then cysteine at position 145 is optionally replaced with serine or threonine; or

j) replacing aspartic acid at position 161 with glutamine, asparagine, serine or threonine, provided that when the replacing amino acid is aspargine, then leucine at position 163 is optionally replaced with serine or threonine,

and physiologically acceptable salts of said polypeptide and said fragment.

5. A FLINT analog comprising a polypeptide having FLINT biological activity, said polypeptide having the amino acid sequence of SEQ ID NO:1 modified by:

a) replacing alanine at position 2, 12, 107, 179 or 209 with threonine;
b) replacing threonine at position 4 or 162 with alanine;
c) replacing valine at position 1 or isoleucine at position 110 with methionine;
d) replacing glutamic acid at position 13 with aspartic acid;
e) replacing arganine at position 17 with tryptophan;
f) replacing alanine at position 75 with proline;
g) replacing serine at positione 102 with leucine;
h) replacing glycine at position 169 with alanine;
i) replacing glutamic acid at position 183 with lysine;
j) replacing glutamine at position 225 with arginine;
k) replacing glycine at position 237 with glutamic acid; or
l) replacing valine at position 270 with glycine,

and physiologically acceptable salts of said polypeptide and said fragment.

6. A FLINT analog comprising a polypeptide having FLINT biological activity, said polypeptide having the amino acid sequence of SEQ ID NO:1 modified by:

a) replacing alanine at position 12 with asparagine and optionally replacing glutamic acid at position 13 with glutamine;
b) replacing arginine at position 34 with asparagine and replacing aspartic acid at position 36 with threonine;
c) replacing arginine at position 35 with asparagine and optionally replacing serine at position 37 with threonine;

d) replacing serine at position 132 with asparagine and optionally replacing serine at position 134 with threonine;

e) replacing aspartic acid at position 194 with asparagine and optionally replacing serine at position 196 with threonine;

f) replacing arginine at position 35 and aspartic acid at position 194 with asparagine;

g) replacing alanine at position 12 with asparagine, optionally replacing glutamic acid at position 13 with glutamine, replacing aspartic acid at position 194 with asparagine and optionally replacing serine at position 196 with threonine;

h) replacing arginine at position 34 with asparagine, replacing aspartic acid at position 36 with threonine, replacing aspartic acid at position 194 with asparagine and optionally replacing serine at position 196 with threonine;

i) replacing arginine at position 35 and aspartic acid at position 194 with asparagine and replacing serine at position 37 and/or position 196 with threonine; or

j) replacing arginine at position 218 with glutamine,

and physiologically acceptable salts of said polypeptide and said fragment.

7. A fragment of a FLINT analog of claims 1 through 6 wherein said fragment is defined by residues 1 through 218 of SEQ ID NO:1.

8. A FLINT analog defined by residues 1 through 218 of SEQ ID NO:1.

9. A FLINT analog defined by residues 1 through 216 of SEQ ID NO:1.

10. A fusion protein represented by the following structural formula:

wherein:


;

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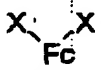
Fc is an Fc fragment of an antibody;

each X is independently the peptide derivative of Claim 1, 2, 3, 4, 5, 6, 7, 10, 11, or 12; and

each polypeptide represented by X is covalently linked at its C-terminus to the N-terminus of one of the polypeptides which form the Fc fragment of the antibody.

11. A fusion protein represented by the following structural formula:

wherein:



;

Fc is an Fc fragment of an antibody;

each X is a protease-resistant FLINT analog; and

each polypeptide represented by X is covalently linked at its C-terminus to the N-terminus of one of the polypeptides which form the Fc fragment of the antibody.

12. A protein of Claim 10 wherein Fc is an Fc fragment from a human antibody.

13. A protein of Claim 11 wherein Fc is an Fc fragment from a human antibody

14. The protein of Claims 12 or 13 wherein Fc lacks the hinge region.

15. A protein of claim 11 wherein said analog comprises SEQ ID NO:1 and wherein arginine at position 218 is replaced by glutamine.

16. A protein of claim 11 said analog comprising the amino acid sequence of SEQ ID NO:1 wherein Arg at position 218 is replaced by an amino acid selected from the group consisting of:

a. any naturally occurring amino acid that is not Arg;

b. any positively charged amino acid that is not Arg;
c. any negatively charged amino acid that is not Arg;
d. any polar uncharged amino acid that is not Arg;
e. any non-polar amino acid that is not Arg; and
f. any amino acid that is Glu, Gln, Ala, Asn, Gly, Ser, Val, or Tyr.

17. A nucleic acid that encodes any one of the FLINT analogs of claims 1 through 16.

18. A vector comprising a nucleic acid of claim 17.

19. Use of a FLINT analog of claims 1 through 16 in the preparation of a medicament useful in treating a disease or disorder selected from the group consisting of acute lung injury, acute respiratory distress syndrome, pulmonary fibrosis, chronic obstructive pulmonary disease, ulcerative colitis, or Crohn's disease.

20. A pharmaceutical composition comprising a FLINT analog of claims 1 through 16 together with one or more pharmaceutically acceptable diluents, carriers or excipients therefor.

PATENT COOPERATION TREATY

# PCT



## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70) 14

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| X-12799 | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/US00/06417 | 20/03/2000 | 30/03/1999 |
| International Patent Classification (IPC) or national classification and IPC<br>C12N15/12 | | |
| Applicant<br>ELI LILLY AND COMPANY et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

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3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 02/10/2000 | 13.06.2001 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized officer<br>Paresce, D<br>Telephone No. +49 89 2399 8995 |

Form PCT/IPEA/409 (cover sheet) (January 1994)

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/06417

## I. Basis f th rep rt

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
**Description, pages:**

1-90 as originally filed

**Claims, No.:**

1-20 with telefax of 26/04/2001

**Drawings, sheets:**

1/2,2/2 as originally filed

**Sequence listing part of the description, pages:**

1-3, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   *(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | |
|---|---|---|
| Novelty (N) | Yes: | Claims 1-20 |
| | No: | Claims |
| Inventive step (IS) | Yes: | Claims 1-20 |
| | No: | Claims |
| Industrial applicability (IA) | Yes: | Claims 1-20 |
| | No: | Claims |

2. Citations and explanations
   **see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
**see separate sheet**

**R It m I**

**Basis of the report**

This International Preliminary Examination Report is based on amended claims 1-20 submitted by a telefax, received on 26.04.01. The amended set of claims is supported by the original disclosure and therefore complies with the requirements of Article 34(2)(b) PCT.

**Re Item V**

**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1) The documents mentioned in this communication are numbered as in the search report, i.e. D1 corresponds to the first document of the search report.

2) **Novelty: Article 33(2) PCT**

D1 describes the human Tumor Necrosis Factor Receptor (TNFR)-6α and 6β proteins. TNFR-6α is identical to FLINT of the present application (see figure 1 of D1). D1 discloses TNFR-6α proteins, nucleic acid molecules encoding human TNFR-6α, vectors, host cells, recombinant methods of producing TNFR-6α, and diagnostic and therapeutic methods involving the use of TNFR-6α proteins (see abstract). D1 also describes variant and mutant TNFR-6α polypeptides. Recombinant DNA techniques to create mutant proteins including single or multiple amino acid substitutions, deletions, additions or fusion proteins are described. For example, N-terminal and C-terminal deletion mutants are described (see p. 24), as well as various mutant TNFR-6α proteins with amino acid substitutions (see p. 25-32). D1 describes the use of amino acid substitutions to produce proteins with desirable improved characteristics such as improved solubility or altered ligand selectivity. Furthermore, D1 discloses fusion proteins formed by combining the TNFR-6α polypeptides and an IgG Fc fusion region peptide to increase the half-life of the polypeptide (see p. 26, 33). Example 3a of D1 describes the cloning and expression of a TNFR-6α-HA fusion protein (see p. 57).

D2 discloses a TNFR homolog called DcR3. DcR3 is identical to FLINT of the present application. D2 discloses nucleic acid molecules encoding DcR3, chimeric molecules and antibodies to DcR3 (see abstract). D2 describes covalent modifications of the DcR3 including adding glycosylation sites to the protein and fusing the DcR3 protein with a tag polypeptide or an immunoglobulin or to the Fc region of an IgG molecule (see p.12-14). D2 also describes methods for introducing nucleotide changes in the DcR3 DNA or amino acid sequence (see p. 15-16). Example 1 of D2 discloses various EST sequences for DcR3 (see p. 36-37) and examples 7-9 disclose a DcR3 polypeptide fused to an epitope tag such as poly-his tags and immunoglobulin tags (Fc regions of IgG).

D3 discloses a TNFR called ZTNFR-5. ZTNFR-5 is also identical to FLINT of the present application. D3 discloses ZTNFR-5 proteins, nucleic acid molecules encoding human ZTNFR-5, vectors, host cells, recombinant methods of producing ZTNFR-5, and diagnostic and therapeutic methods involving the use of ZTNFR-5 proteins (see p. 1-11). D3 also describes methods of making multiple amino acid substitutions in the ZTNFR-5 amino acid sequence (see p. 25-33). D3 discloses soluble ZTNFR-5 receptors used to form fusion proteins with human Ig, or to form His-tagged proteins (see p. 43, example 3).

The subject-matter of claims 1-20 has not been made available to the public by any of the available prior art documents and can therefore be regarded as novel.

2) **Inventive Step: Article 33(3) PCT**

D1, D2 or D3 are regarded as being the closest prior art to the subject-matter of these claims.

The subject-matter of claims 1-20 consists in the provision of polypeptide analogs of FLINT, polynucleotide molecules encoding the FLINT analogs and uses thereof. The FLINT analogs of the present application include polypeptides having the amino acid sequence of FLINT (disclosed in D1, D2 or D3) modified at one or more positions with amino acid substitutions, deletions or additions, and fragments thereof. It is stated on p. 2-3 of the present application that the claimed FLINT analogs are believed to have improved properties compared with FLINT

such as greater potency, longer *in vivo* half lives, decreased aggregation and increased solubility. The present application also claims Fc-FLINT fusion proteins. It is disclosed in the present application that FLINT undergoes proteolysis *in vivo* to produce two peptide fragments. Protease resistant FLINT analogs can be produced that are more resistant to proteolysis between residues 218 and 219 of SEQ ID NO: 1 by one or more amino acid substitutions, deletions or additions of the FLINT full-length sequence (see p. 16-19). It is stated that preferably these changes occur in the region from about position 214 through position 222 of SEQ ID NO:1 (p. 17). The prior art does not disclose the proteolytic processing of FLINT at residue 218 nor that protease resistant FLINT analogs can be produced by mutations of the FLINT amino acid sequence in the region around residue 218.

At the priority date of the present application, FLINT analogs and methods of making mutant FLINT polypeptides had already been disclosed in the prior art. D1, for example, describes several variant and mutant TNFR-6α polypeptides. N-terminal and C-terminal deletion mutants are described (see p. 24), as well as various mutant TNFR-6α proteins with amino acid substitutions (see p. 25-32). D1 describes the use of amino acid substitutions to produce proteins with desirable improved characteristics such as improved solubility or altered ligand selectivity. Furthermore, D1 discloses fusion proteins formed by combining the TNFR-6α polypeptides and an IgG Fc fusion region peptide to increase the half-life of the polypeptide (see p. 26, 33). Example 3a of D1 describes the cloning and expression of a TNFR-6α-HA fusion protein (see p. 57).

The prior art, however, does not disclose the specific analogs of the present application and the IPEA is of the opinion that the subject-matter of claims 1-20 cannot be derived from the available prior art in an obvious manner and therefore complies with the requirements of Article 33(3) PCT.

**Re Item VI**

**Certain documents cited**

Certain published documents (Rule 70.10)

| Application No Patent No | Publication date *(day/month/year)* | Filing date *(day/month/year)* | Priority date *(valid claim)* *(day/month/year)* |
|---|---|---|---|
| WO 00/34782 | 15.06.00 | 07.12.99 | 09.12.98 |

## VIII. Certain observations on the international application

### 1) Clarity: Article 6 PCT

Article 6 PCT requires amongst other things that the claims, which define the matter for which protection is sought (i.e. the object of invention) be clear. This has to be interpreted as meaning not only that a claim from a technical point of view must be comprehensible, but also that it must define clearly the object of the invention, that is to say, it must indicate all the essential features thereof. The essential features are regarded as all features which are necessary to obtain the desired effect, or differently expressed, those features which are necessary to solve the technical problem with which the application is concerned. In other words, all technical features which enable the skilled person to put the claimed matter into practice without undue burden i.e. without experimentation or without application of inventive skill.

In the present case, the subject-matter of claims 11, 13-14 is not disclosed in a manner sufficiently clear and complete for a person skilled in the art to put the claimed matter into practice. Claims 11, 13-14 refer to a "protease-resistant FLINT analog". The use of an internal arbitrary designation of a protein is meaningless to the person skilled in the art and does not constitute a definition through technical means as required by Article 6 PCT. The IPEA considers TNFR-6α, DcR3, ZTNFR-5 to be "FLINT analogs". Furthermore, the term, "protease-resistant" is vague and merely paraphrases the technical problem with which the application is concerned. The claims attempt to define the subject-matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result should be added. The claimed protein must be clearly and unambiguously characterized e.g. by reference to technical features, (sequence information) in order to satisfy the requirements of Article 6 PCT.

We Claim:

1. A FLINT analog comprising a polypeptide or a fragment of said polypeptide having FLINT biological activity, said polypeptide having the amino acid sequence of SEQ ID NO:1 modified by:
   a) replacing tryptophan at position 53 with aspartic acid;
   b) replacing threonine at position 88 with proline;
   c) replacing alanine at position 107 with serine, aspartic acid, glutamic acid or threonine;
   d) replacing isoleucine at position 110 with threonine or glutamic acid; or
   e) replacing proline at position 104 with serine,
   and physiologically acceptable salts of said polypeptide and said fragment.

2. A FLINT analog comprising a polypeptide or a fragment of said polypeptide having FLINT biological activity, said polypeptide having the amino acid sequence of SEQ ID NO:1 modified by:
   a) replacing alanine at position 2 or position 12 with asparagine;
   b) replacing proline at position 25, position 38, position 126 or position 171 with asparagine;
   c) replacing arginine at position 35 with asparagine;
   d) replacing serine at position 37 with asparagine and proline at position 38 with any other naturally occurring amino acid;
   e) replacing serine at position 166 with asparagine;
   f) replacing leucine at position 172 with asparagine;

g) replacing aspartic acid at position 194 with asparagine; or

h) replacing threonine at position 114 with asparagine and proline at position 115 with any naturally occurring amino acid;

and physiologically acceptable salts of said polypeptide and said fragment.

3. A FLINT analog comprising a polypeptide or a fragment of said polypeptide having FLINT biological activity, said polypeptide having the amino acid sequence of SEQ ID NO:1 modified by:

a) replacing asparagine at position 63 with tryptophan;

b) replacing glycine at position 67 with aspartic acid and alanine at position 94 or glycine at position 95 with tyrosine;

c) replacing arginine at position 69 with glutamic acid;

d) replacing arginine at position 82 with glutamic acid or threonine;

e) replacing alanine at position 94 with tryosine and glycine at position 95 with aspartic acid;

f) replacing phenylalanine at position 96 with glutamine;

g) replacing alanine at position 101 with threonine; or

h) replacing glycine at position 95 with aspartic acid;

and physiologically acceptable salts of said polypeptide and said fragment.

4. A FLINT analog comprising a polypeptide or a fragment of said polypeptide having FLINT biological activity, said polypeptide having the amino acid sequence of SEQ ID NO:1 modified by:

a) replacing arginine at position 10 with glutamine, asparagine, serine or threonine, provided that when the replacing amino acid is asparagine, then alanine at position 12 is optionally replaced with serine or threonine;

b) replacing glutamic acid at position 13 with glutamine, asparagine, serine or threonine, provided that when the replacing amino acid is asparagine, then glycine at position 15 is optionally replaced with serine or threonine;

c) replacing glutamic acid at position 16 with glutamine, asparagine, serine or threonine, provided that when the replacing amino acid is asparagine, then leucine at position 18 is optionally replaced with serine or threonine;

d) replacing arginine at position 17 with glutamine, asparagine, serine or threonine, provided that when the replacing amino acid is asparagine, then valine at position 19 is optionally replaced with serine or threonine;

e) replacing arginine at position 31 with glutamine, asparagine, serine or threonine, provided that when the replacing amino acid is asparagine, then cysteine at position 33 is optionally replaced with serine or threonine;

f) replacing arginine at position 34 with glutamine, asparagine, serine or threonine, provided that when the replacing amino acid is asparagine, then

aspartic acid at position 36 is optionally replaced with serine or threonine;

g) replacing arginine at position 35 with glutamine, asparagine, serine or threonine;

h) replacing aspartic acid at position 36 with glutamine, asparagine, serine or threonine, provided that when the replacing amino acid is asparagine, then proline at position 38 is optionally replaced with serine or threonine;

i) replacing arginine at position 143 with glutamine, asparagine, serine or threonine, provided that when the replacing amino acid is asparagine, then cysteine at position 145 is optionally replaced with serine or threonine; or

j) replacing aspartic acid at position 161 with glutamine, asparagine, serine or threonine, provided that when the replacing amino acid is aspargine, then leucine at position 163 is optionally replaced with serine or threonine,

and physiologically acceptable salts of said polypeptide and said fragment.

5. A FLINT analog comprising a polypeptide or fragment of said polypeptide having FLINT biological activity, said polypeptide having the amino acid sequence of SEQ ID NO:1 modified by:

a) replacing alanine at position 2, 12, 107, 179 or 209 with threonine;

b) replacing threonine at position 4 or 162 with alanine;

c) replacing valine at position 1 or isoleucine at position 110 with methionine;

d) replacing glutamic acid at position 13 with aspartic acid;

e) replacing arganine at position 17 with tryptophan;

f) replacing alanine at position 75 with proline;

g) replacing serine at positione 102 with leucine;

h) replacing glycine at position 169 with alanine;

i) replacing glutamic acid at position 183 with lysine;

j) replacing glutamine at position 225 with arginine;

k) replacing glycine at position 237 with glutamic acid; or

l) replacing valine at position 270 with glycine,

and physiologically acceptable salts thereof.

6. A FLINT analog comprising a polypeptide or a fragment of said polypeptide having FLINT biological activity, said polypeptide having the amino acid sequence of SEQ ID NO:1 modified by:

a) replacing alanine at position 12 with asparagine and optionally replacing glutamic acid at position 13 with glutamine;

b) replacing arginine at position 34 with asparagine and replacing aspartic acid at position 36 with threonine;

c) replacing arginine at position 35 with asparagine and optionally replacing serine at position 37 with threonine;

d) replacing serine at position 132 with asparagine and optionally replacing serine at position 134 with threonine;

e) replacing aspartic acid at position 194 with asparagine and optionally replacing serine at position 196 with threonine;

f) replacing arginine at position 35 and aspartic acid at position 194 with asparagine;

g) replacing alanine at position 12 with asparagine, optionally replacing glutamic acid at position 13 with glutamine, replacing aspartic acid at position 194 with asparagine and optionally replacing serine at position 196 with threonine;

h) replacing arginine at position 34 with asparagine, replacing aspartic acid at position 36 with threonine, replacing aspartic acid at position 194 with asparagine and optionally replacing serine at position 196 with threonine;

i) replacing arginine at position 35 and aspartic acid at position 194 with asparagine and replacing serine at position 37 and/or position 196 with threonine; or

j) replacing arginine at position 218 with glutamine,

and physiologically acceptable salts thereof.

7. A FLINT fragment of any one of claims 1 through 6 wherein said fragment comprises residues 1 through 218 of SEQ ID NO:1.

8. A polypeptide fragment of FLINT that is biologically active *in vivo* and/or *in vitro*.

9. A FLINT fragment, as in claim 8 wherein said biological activity is selected from the group consisting of:

a. binding FasL *in vivo* or *in vitro*;

b. binding LIGHT *in vivo* or *in vitro*; or

c. treatment of a disorder that can be treated with FLINT.

10. A biologically active FLINT polypeptide fragment as in Claim 8 wherein said polypeptide comprising residues 1 through 218 of SEQ ID NO:1.

11. A biologically active polypeptide fragment as in Claim 8 wherein said polypeptide consists essentially of residues 1 through 218 of SEQ ID NO:1.

12. A FLINT polypeptide fragment as in Claim 8 wherein said fragment comprises residues 1 through 216 of SEQ ID NO:1.

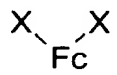
13. A FLINT polypeptide fragment as in claim 11 produced by enzymatic digestion of FLINT.

14. A FLINT polypeptide fragment as in claim 13 produced by enzymatic digestion of FLINT with a serine protease.

15. A FLINT polypeptide fragment as in Claim 14 wherein said protease is thrombin or trypsin.

16. A FLINT fragment as in claims 10 or 11 produced by recombinant means.

17. A fusion protein represented by the following structural formula:




;

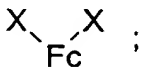
wherein:

Fc is an Fc fragment of an antibody;

each X is independently the peptide derivative of Claim 1, 2, 3, 4, 5, 6, 7, 10, 11, or 12; and

each polypeptide represented by X is covalently linked at its C-terminus to the N-terminus of one of the polypeptides which form the Fc fragment of the antibody.

18. A fusion protein represented by the following structural formula:



wherein:

Fc is an Fc fragment of an antibody;

each X is a protease-resistant FLINT analog; and

each polypeptide represented by X is covalently linked at its C-terminus to the N-terminus of one of the polypeptides which form the Fc fragment of the antibody.

19. The protein of Claim 17 wherein Fc is an Fc fragment from a human antibody.

20. The protein of Claim 18 wherein Fc is an Fc fragment from a human antibody.

21. The protein of Claims 19 or 20 wherein Fc lacks the hinge region.

22. A protein of claim 18 wherein said analog comprises SEQ ID NO:1 and wherein arginine at position 218 is replaced by glutamine.

23. A protein of claim 18 wherein said analog having an amino acid sequence that is at least about 50% identical with residues 214 through 222 of SEQ ID NO:1.

24. A protein of claim 18 said analog comprising the amino acid sequence of SEQ ID NO:1 wherein Arg at position 218 is replaced by an amino acid selected from the group consisting of:

a. any naturally occurring amino acid that is not Arg;
b. any positively charged amino acid that is not Arg;
c. any negatively charged amino acid that is not Arg;
d. any polar uncharged amino acid that is not Arg;
e. any non-polar amino acid that is not Arg; and
f. any amino acid that is Glu, Gln, Ala, Gly, Ser, Val, or Tyr.

25. A nucleic acid that encodes any one of the FLINT analogs of claims 1 through 6.

26. A nucleic acid that encodes any one of the FLINT fragment of claims 7 through 12.

27. A nucleic acid that encodes a fusion protein of claim 17.

28. A nucleic acid that encodes a fusion protein of claim 18.

29. A vector comprising a nucleic acid of claim 25.

30. A vector comprising a nucleic acid of claim 26.

31. A vector comprising a nucleic acid of claim 27.

32. A vector comprising a nucleic acid of claim 28.

33. A host cell transformed with a vector of claim 29.

34. A host cell transformed with a vector of claim 30.

35. A host cell transformed with a vector of claim 31.

36. A host cell transformed with a vector of claim 32.

37. A polydeoxynucleotide or a fragment thereof, said polydeoxynucleotide having the nucleotide sequence of SEQ ID NO:2 modified by:

a) replacing the codon encoding tryptophan at positions 157-59 with a codon encoding aspartic acid;

b) replacing the codon encoding threonine at positions 262-264 with a codon encoding proline;

c) replacing the codon encoding alanine at positions 319-21 with a codon encoding serine, aspartic acid, glutamic acid or threonine;

d) replacing the codon encoding isoleucine at positions 328-30 with a codon encoding threonine or glutamic acid; or

e) replacing the codon encoding proline at positions 310-12 with a codon encoding serine,

said fragment comprising deoxynucleotides 145-495 of the polydeoxynucleotide.

38. A polydeoxynucleotide or a fragment thereof, said polydeoxynucleotide having the nucleotide sequence of SEQ ID NO:2 modified by:

a) replacing the codon encoding alanine at positions 4-6 or positions 34-36 with a codon encoding asparagine;

b) replacing the codon encoding proline at positions 73-75 with a codon encoding asparagine;

c) replacing the codon encoding arginine at positions 103-105 with a codon encoding asparagine;

d) replacing the codon encoding serine at positions 109-111 with a codon encoding asparagine and replacing the codon encoding proline at positions 112-114 with a codon encoding any other naturally occurring amino acid;

e) replacing the codon encoding proline at positions 112-114 with a codon encoding asparagine;

f) replacing the codon encoding proline at positions 376-378 with a codon encoding asparagine;

g) replacing the codon encoding serine at positions 496-498 with a codon encoding asparagine;

h) replacing the codon encoding proline at positions 511-513 with a codon encoding asparagine;

i) replacing the codon encoding leucine at positions 514-516 with a codon encoding asparagine;

j) replacing the codon encoding aspartic acid at positions 580-582 with a codon encoding asparagine;

k) replacing the codon encoding threonine at positions 340-342 with a codon encoding asparagine and replacing the codon encoding proline at positions

343-345 with a codon encoding any naturally occurring amino acid; or

l) replacing the codon encoding arginine at position 652-654 with a codon encoding asparagine,

said fragment comprising deoxynucleotides 145-495 of the polydeoxynucleotide.

39. A polydeoxynucleotide or a fragment thereof, said polydeoxynucleotide having the nucleotide sequence of SEQ ID NO:2 modified by:

a) replacing the codon encoding asparagine at positions 187-189 with a codon encoding tryptophan;

b) replacing the codon encoding glycine at positions 199-201 with a codon encoding aspartic acid and replacing the codon encoding alanine at positions 280-282 or glycine at positions 283-285 with a codon encoding tyrosine;

c) replacing the codon encoding arginine at positions 205-07 with a codon encoding glutamic acid;

d) replacing the codon encoding arginine at positions 244-246 with a codon encoding glutamic acid or threonine;

e) replacing the codon encoding alanine at positions 280-282 with a codon encoding tyrosine and replacing the codon encoding glycine at positions 283-285 with a codon encoding aspartic acid;

f) replacing the codon encoding phenylalanine at positions 286-288 with a codon encoding glutamine;

g) replacing the codon encoding alanine at positions 301-303 with a codon encoding threonine; or

i) replacing the codon encoding glycine at positions 283-285 with a codon encoding aspartic acid,

said fragment comprising deoxynucleotides 145-495 of the polydeoxynucleotide.

40. A polydeoxynucleotide or a fragment thereof, said polydeoxynucleotide having the nucleotide sequence of SEQ ID NO:2 modified by:

a) replacing the codon encoding arginine at positions 28-30 with a codon encoding glutamine, asparagine, serine or threonine, provided that when the replacing codon encodes asparagine, then the codon encoding alanine at positions 34-36 is optionally replaced with a codon encoding serine or threonine;

b) replacing the codon encoding glutamic acid at positions 37-39 with a codon encoding glutamine, asparagine, serine or threonine, provided that when the replacing codon encodes asparagine, then the codon encoding glycine at positions 43-45 is optionally replaced with a codon encoding serine or threonine;

c) replacing the codon encoding glutamic acid at positions 46-48 with a codon encoding glutamine, asparagine, serine or threonine, provided that when the replacing codon encodes asparagine, then the codon encoding leucine at positions 52-54 is optionally replaced with a codon encoding serine or threonine;

d) replacing the codon encoding arginine at positions 49-51 with a codon encoding glutamine, asparagine, serine or threonine, provided that when the

replacing codon encodes asparagine, then the codon encoding valine at positions 55-57 is optionally replaced with a codon encoding serine or threonine;

e) replacing the codon encoding arginine at positions 91-93 with a codon encoding glutamine, asparagine, serine or threonine, provided that when the replacing codon encodes asparagine, then the codon encoding cysteine at positions 97-99 is optionally replaced with a codon encoding serine or threonine;

f) replacing the codon encoding arginine at positions 100-102 with a codon encoding glutamine, asparagine, serine or threonine, provided that when the replacing codon encodes asparagine, then the codon encoding aspartic acid at positions 106-108 is optionally replaced with a codon encoding serine or threonine;

g) replacing the codon encoding arginine at positions 103-105 with a glutamine, asparagine, serine or threonine;

h) replacing the codon encoding aspartic acid at positions 106-108 with a codon encoding glutamine, asparagine, serine or threonine, provided that when the replacing codon encodes asparagine, then the codon encoding proline at positions 112-114 is optionally replaced with a codon encoding serine or threonine;

i) replacing the codon encoding arginine at positions 427-429 with a codon encoding glutamine, asparagine, serine or threonine, provided that when the replacing codon encodes asparagine, then

the codon encoding cysteine at positions 433-435 is optionally replaced with a codon encoding serine or threonine; or

j) replacing the codon encoding aspartic acid at positions 481-483 with a codon encoding glutamine, asparagine, serine or threonine, provided that when the replacing codon encodes aspargine, then the codon replacing leucine at positions 487-489 is optionally replaced with a codon encoding serine or threonine,

said fragment comprising deoxynucleotides 145-495 of the polydeoxynucleotide.

41. A polydeoxynucleotide or a fragment thereof, said polydeoxynucleotide having the nucleotide sequence of SEQ ID NO:2 modified by:

a) replacing the codong encoding alanine at positions 4-6, 34-36, 319-321, 535-537 or 625-627 with a condon encoding threonine;

b) replacing the codon encoding threonine at position 10-12 or 484-486 with a codon encoding alanine;

c) replacing the codon encoding valine at position 1-3 or isoleucine at position 328-330 with a condon encoding methionine;

d) replacing the codon encoding glutamic acid at position 37-39 with a codon encoding aspartic acid;

e) replacing the codon encoding arganine at position 49-51 with a codon encoding tryptophan;

f) replacing the codon encoding alanine at position 223-225 with a codon encoding proline;

g) replacing the codon encoding serine at position 304-306 with a codon encoding leucine;

h) replacing the codon encoding glycine at position 505-507 with a codon encoding alanine;

i) replacing the codon encoding glutamic acid at position 547-549 with a codon encoding lysine;

j) replacing the codon encoding glutamine at position 673-675 with a codon encoding arginine;

k) replacing the codon encoding glycine at position 709-711 with a codon encoding glutamic acid; or

m) replacing the codon encoding valine at position 808-810 with a codon encoding glycine,

said fragment comprising deoxynucleotides 145-495 of the polydeoxynucleotide.

42. A vector comprising a polydeoxynucleotide of any one of Claims 37, 38, 39, 40, or 41.

43. Use of a FLINT analog to treat a disease or condition in a patient in need thereof.

44. A method of treatment for a patient suffering from a disease or condition relating to the binding of FasL to Fas, or the binding of LIGHT to LTβR and/or TR2/HVEM, comprising the administration of a therapeutically effective amount of a FLINT analog.

45. A method as in claim 44 wherein said analog is a FLINT fragment comprising residues 1 through 218 of SEQ ID NO:1.

46. A method as in claim 44 wherein said analog comprises a protease-resistant FLINT Fc fusion protein.

47. A method as in claim 44 wherein said disease is selected from the group consisting of acute lung injury, acute respiratory distress syndrome, pulmonary fibrosis, chronic obstructive pulmonary disease, ulcerative colitis, or Crohn's disease.

48. Use of a FLINT analog in the preparation of a medicament useful in treating a disease or disorder related to abnormal apoptosis.

49. Use of a FLINT analog as in claim 48 wherein said disorder is selected from the group consisting of acute lung injury, acute respiratory distress syndrome, pulmonary fibrosis, chronic obstructive pulmonary disease, ulcerative colitis, or Crohn's disease.

50. A pharmaceutical composition comprising a FLINT analog together with one or more pharmaceutically acceptable diluents, carriers or excipients therefor.

51. A pharmaceutical composition as in claim 50 wherein said analog comprises FLINT fragment 1 through 218 of SEQ ID NO:1.

52. A pharmaceutical composition as in claim 50 wherein said analog comprises a protease-resistant FLINT-Fc fusion protein.